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Research

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OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Review of Data for the Carcinogenicity of Linuron

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In reply to your February 17, 1983 request, I have prepared a review of the available data regarding the carcinogenicity of linuron.

I have examined the material which Dr. J. Holder (HED, TS-769) summarized concerning the two-year rat feeding study of linuron by DuPont (1980) and agree that there is a positive interstitial cell (ISC) adenoma response in the testes of male Charles River CD rats. The major data from his report are presented in Table 1, which shows a statistically significant increase in the incidence of ISC adenomas in male rats at both 125 and 625 ppm in the diet. The historical control values for the incidence of ISC adenomas from five different studies performed at DuPont's Haskell Laboratory during the same time period as the 1980 rat study averaged about a 17% incidence (range was 8.6 to 20.3%). This historical data was presented in a letter from Dr. R. Everett of DuPont to Dr. J. Holder of EPA (dated June 10, 1982).

I have also reviewed the chronic study in mice fed linuron (Haskell Laboratory Report No. 758-82). Linuron (INZ-326) was fed to male and

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TABLE 1. INCIDENCE OF INTERSTITIAL CELL ADENOMAS IN THE TESTES IN MALE CHARLES RIVER CD RATS FED LINURON FOR 2 YEARS
(adapted from Holder September 15, 1982)

Dose (ppm)	No. of Rats in 2-Year Test*	Incidence (No. Rats with Tumors/ No. Rats Examined)
0	70	4/70 (5.7%)
50	69	9/69 (13.0%)
125	70	20/70 (28.6%) $P = 2.7 \times 10^{-4}$†
625	70	37/70 (52.9%) $P = 2.3 \times 10^{-10}$†

*These numbers do not include the 10 rats/group sacrificed at one year, since none of these rats had ISC adenomas.
†P values calculated by the Fisher's Exact Test.

female Charles Riv[illegible] mice for 24 months at l[illegible] of 0, 5, 150, and 1500 ppm in the diet. Eight groups of 80 mice each were used in this study. All animals were subjected to both gross and microscopic pathological examination when either terminal sacrifice was reached (24 months) or when found dead or sacrificed in extremis. Selected animals during the study were utilized for hematological examination.

Survival data indicated no real differences between control and treated groups. At the 1500 ppm dose, mean body weight and mean body weight gain were decreased in both male and female mice throughout the experiment. The values of methemoglobin were increased in both male and female treated mice; this increase was related to compound administration. The mean absolute and relative liver weights were increased in female mice in the 1500 ppm dose group.

Microscopic examination of the tissues and organs of these mice indicated that abnormalities were present in the livers and spleens of male and female animals which appeared to be related to compound administration. Slightly increased incidences of hemosiderosis of the spleen were reported for both male and female mice in the 1500 ppm dose group. Compound-related effects in the liver included hepatocytomegaly, hepatocellular cytoplasmic alteration, hepatocellular vacuolization, hemorrhage, and necrosis. A statistically-significant increase was reported for the incidence of hepatocellular adenomas of male mice in the 50 ppm dose group only and of female mice in the 1500 ppm dose group, as seen in Table 2. Also, no significant increases were presented for

TABLE 2. INCIDENCE OF LIVER TUMORS IN MALE AND FEMALE CHARLES RIVER CD-1 MICE FED LINURON FOR 24 MONTHS
(adapted from DuPont 1982)

Diagnoses	Doses			
	0 ppm	50 ppm	150 ppm	1500 ppm
		MALE		
Hepatocellular Adenoma (HA)	9/79(11.4%)	18/80(22.5%) P = 0.048*	10/80(12.5%)	16/78(20.5%)
Hepatocellular Carcinoma (HC)	4/79(5.1%)	3/80(2.8%)	3/80(3.8%)	2/78(2.6%)
Combined (HA and HC)	13/79(16.5%)	21/80(26.3%)	13/80(16.3%)	18/78(23.1%)
		FEMALE		
Hepatocellular Adenoma (HA)	5/79(6.3%)	6/79(7.6%)	8/76(10.5%)	20/80(25%) P = 0.001*
Hepatocellular Carcinoma (HC)	1/79(1.3%)	1/79(1.3%)	3/76(3.9%)	2/80(2.5%)
Combined (HA and HC)	6/79(7.6%)	7/79(8.9%)	11/76(14.5%)	22/80(27.5%) P = 8.2x10^{-4}*

*P values calculated by the Fisher's Exact Test.

hepatocellular carcinomas only in either sex at any dosage.

Dr. J. Fowle of the Reproductive Effects Assessment Group (REAG) stated that the data are inadequate for assessing the mutagenic potential of linuron because of the limited tests conducted (memo to Dr. R. McGaughy, dated May 13, 1983).

One can thus conclude that the weight-of-evidence (based on IARC criteria) for the carcinogenicity of linuron is limited for animals and is in group 3 overall, based on the absence of any human data, a positive response for benign interstitial cell adenomas of the testes in male Charles River CD rats and benign hepatocellular adenomas in male and female Charles River CD-1 mice. A mechanism of oncogenesis cannot be inferred for linuron with the present data. Since a mechanism(s) is (are) not known, it is a moot point to question how such a mechanism(s) might affect the assessment of oncogenic risks at appropriate levels of human exposure. Further studies that might elucidate some mechanism(s) for the carcinogenicity of linuron should include long-term carcinogenicity studies in animals with simultaneous hormonal determinations during these studies.

Dr. T. Thorslund of the CAG is reviewing the quantitative aspects of performing a risk assessment for the carcinogenicity of linuron, including a review of Dr. B. Litt's (HED) analysis of the rat data.